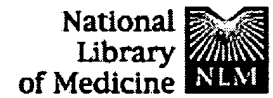

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ARTICLES

Therapy of murine tumors with tumor peptide-pulsed dendritic cells: dependence on T cells, B7 costimulation, and T helper cell 1-associated cytokines

L Zitvogel, JI Mayordomo, T Tjandrawan, AB DeLeo, MR Clarke, MT Lotze and WJ Storkus
Department of Surgery, University of Pittsburgh, Pennsylvania 15261, USA.

Antigen presentation by host dendritic cells (DC) is critical for the initiation of adaptive immune responses. We have previously demonstrated in immunogenic murine tumor models that bone marrow (BM)- derived DC pulsed ex vivo with synthetic tumor-associated peptides, naturally expressed by tumor cells, serve as effective antitumor vaccines, protecting animals against an otherwise lethal tumor challenge (Mayordomo, J.I., T. Zorina, W.J. Storkus, C. Celluzzi, L.D. Falo, C.J. Melief, T. Ildstad, W.M. Kast, A.B. DeLeo, and M.T. Lotze. 1995. Nature Med. 1:1297-1302). However, T cell-defined epitopes have not been identified for most human cancers. To explore the utility of this approach in the treatment of tumors expressing as yet uncharacterized epitopes, syngeneic granulocyte/macrophage colony- stimulating factor-stimulated and BM-derived DC, pulsed with unfractionated acid-eluted tumor peptides (Storkus, W.J., H.J. Zeh III, R.D. Salter, and M.T. Lotze. 1993. J. Immunother. 14:94-103) were used to treat mice bearing spontaneous, established tumors. The adoptive transfer of 5 x 10(5) tumor peptide-pulsed DC dramatically suppressed the growth of weakly immunogenic tumors in day 4 to day 8 established MCA205 (H-2b) and TS/A (H-2d) tumor models, when applied in three biweekly intravenous injections. Using the immunogenic C3 (H-2b) tumor model in B6 mice, tumor peptide-pulsed DC therapy resulted in the erradication of established d14 tumors and long-term survival in 100% of treated animals. The DC-driven antitumor immune response was primarily cell mediated since the transfer of spleen cells, but not sera, from immunized mice efficiently protected sublethally irradiated naive mice against a subsequent tumor challenge. Furthermore, depletion of either CD4+ or CD8+ T cells from tumor-bearing mice before therapy totally suppressed the therapeutic efficacy of DC pulsed with tumor- derived peptides. Costimulation of the host cell-mediated antitumor immunity was critical since inoculation of the chimeric fusion protein CTLA4-Ig virtually abrogated the therapeutic effects of peptide-pulsed DC in vivo. The analysis of the cytokine pattern in the draining lymph nodes and spleens of tumor-bearing mice immunized with DC pulsed with tumor-eluted peptides revealed a marked upregulation of interleukin (IL) 4 and interferon (IFN) gamma production, as compared with mice immunized with DC alone or DC pulsed with irrelevant peptides. DC- induced antitumor effects were completely blocked by coadministration of neutralizing monoclonal antibody directed against T helper cell

1- associated cytokines (such as IL-12, tumor necrosis factor alpha, IFN- gamma), and eventually, but not initially, blocked by anti-mIL-4 mAb. Based on these results, we believe that DC pulsed with acid-eluted peptides derived from autologous tumors represents a novel approach to the treatment of established, weakly immunogenic tumors, and serves as a basis for designing clinical trials in cancer patients.

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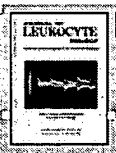

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☐ 1: Cancer Res 2001 Dec 1;61(23):8513-9

Vaccination of pediatric solid tumor patients with tumor lysate-pulsed dendritic cells can expand specific T cells and mediate tumor regression.

Geiger JD, Hutchinson RJ, Hohenkirk LF, McKenna EA, Yanik GA, Levine JE, Chang AE, Braun TM, Mule JJ.

Department of Surgery, Section of Pediatric Surgery, Section of General Surgery, the Tumor Immunology and Immunotherapy Program, Ann Arbor, Michigan 48109-0245, USA. jgeiger@umich.edu

Dendritic cells (DCs) have been shown to be a promising adjuvant for inducing immunity to cancer. We evaluated tumor lysate-pulsed DC in a Phase I trial of pediatric patients with solid tumors. Children with relapsed solid malignancies who had failed standard therapies were eligible. The vaccine used immature DC (CD14-, CD80+, CD86+, CD83-, and HLA-DR+) generated from peripheral blood monocytes in the presence of granulocyte/monocyte colony-stimulating factor and interleukin-4. These DC were then pulsed separately with tumor cell lysates and the immunogenic protein keyhole limpet hemocyanin (KLH) for 24 h and then combined. A total of 1 x 10(6) to 1 x 10(7) DC are administered intradermally every 2 weeks for a total of three vaccinations. Fifteen patients (ages 3-17 years) were enrolled with 10 patients completing all vaccinations. Leukapheresis yields averaged 2.8 x 10(8) peripheral blood mononuclear cells (PBMC)/kg, and DC yields averaged 10.9% of starting PBMC. Patients with neuroblastoma, sarcoma, and renal malignancies were treated without obvious toxicity. Delayed-type hypersensitivity (DTH) response was detected in 7 of 10 patients for KLH and 3 of 6 patients for tumor lysates. Priming of T cells to KLH was seen in 6 of 10 patients and to tumor in 3 of 7 patients as demonstrated by specific IFN-gamma-secreting T cells in unstimulated PBMCs. Significant regression of multiple metastatic sites was seen in 1 patient. Five patients showed stable disease, including 3 who had minimal disease at time of vaccine therapy and remain free of tumor with 16-30 months follow-up. Our results demonstrate that it is feasible to generate large numbers of functional DC from pediatric patients even in those highly pretreated and with a large tumor burden. The DC can

be administered in an outpatient setting without any observable toxicity. Most importantly, we have demonstrated the ability of the tumor lysate/KLH-pulsed DC to generate specific T-cell responses and to elicit regression of metastatic disease.

Publication Types:
- Clinical Trial
- Clinical Trial, Phase I

MeSH Terms:
- Adolescence
- Child
- Child, Preschool
- Dendritic Cells/immunology*
- Female
- Hemocyanin/immunology
- Human
- Hypersensitivity, Delayed/immunology
- Immunotherapy, Adoptive*
- Interferon Type II/secretion
- Leukapheresis
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- Neoplasms/immunology*
- Support, Non-U.S. Gov't
- Support, U.S. Gov't, P.H.S.
- T-Lymphocytes/secretion
- T-Lymphocytes/immunology*
- Vaccination

Substances:
- Hemocyanin
- Interferon Type II
- keyhole-limpet hemocyanin

Grant support:
- 1-R29-CA-77471-01/CA/NCI
- 5PO1 CA 59327/CA/NCI
- MO1-RR00042/RR/NCRR
- T32-CA-09672/CA/NCI

PMID: 11731436 [PubMed - indexed for MEDLINE]

1: Cancer Immunol Immunother 2001 Aug;50(6):321-7

The generation of anti-tumoral cells using dentritic cells from the peripheral bloood of patients with malignant brain tumors.

Yoshida S, Morii K, Watanabe M, Saito T, Yamamoto K, Tanaka R.

Department of Neurosurgery, Niigata Cancer Center Hospital, Japan.
brain@niigata-cc.niigata.niigata.jp

Dendritic cells (DCs) can be the principal initiators of antigen-specific immune responses. We analyzed the in vitro-responses against brain tumor cells using DCs from the peripheral blood of patients with brain tumors. Peripheral blood mononuclear cells (PBMC) were obtained from 19 patients with malignant brain tumors: 12 metastatic brain tumors of lung adenocarcinoma, 7 high-grade astrocytomas. PBMC were cultured with 100 ng/ml of GM-CSF and 10 ng/ml of IL-4 for 5 7 days in order to produce mature DCs. The autologous tumor lysate (5 mg/ml, containing 1 x 10(6) cells) was then added to the cultured DCs. Using the DCs generated by these treatments, we assessed the changes that occurred in their immune responses against brain tumor via 51Cr-release and lymphocyte proliferation assays. We found that the matured DCs displayed the typical surface phenotype of CD3+, CD45+, CD80+ and CD86+. After the pulsation treatment with tumor lysate, DCs were found to have strong cytotoxic T lymphocyte activity, showing 42.5+12.7% killing of autologous tumor cells. We also found an enhancement of allogeneic T cell proliferation after pulsing the DC with tumor lysate. These data support the efficacy of DC-based immunotherapy for patients with malignant brain tumors.

PMID: 11570586 [PubMed - indexed for MEDLINE]

1: Nat Med 2002 Aug;8(8):808-15

nature medicine

Smac agonists sensitize for Apo2L/TRAIL- or anticancer drug-induced apoptosis and induce regression of malignant glioma in vivo.

Fulda S, Wick W, Weller M, Debatin KM.

University Children's Hospital, Ulm, Germany.

A major concern in cancer therapy is resistance of tumors such as glioblastoma to current treatment protocols. Here, we report that transfer of the gene encoding second mitochondria-derived activator of caspase (Smac) or Smac peptides sensitized various tumor cells in vitro and malignant glioma cells in vivo for apoptosis induced by death-receptor ligation or cytotoxic drugs. Expression of a cytosolic active form of Smac or cell-permeable Smac peptides bypassed the Bcl-2 block, which prevented the release of Smac from mitochondria, and also sensitized resistant neuroblastoma or melanoma cells and patient-derived primary neuroblastoma cells ex vivo. Most importantly, Smac peptides strongly enhanced the antitumor activity of Apo-2L/tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) in an intracranial malignant glioma xenograft model in vivo. Complete eradication of established tumors and survival of mice was only achieved upon combined treatment with Smac peptides and Apo2L/TRAIL without detectable toxicity to normal brain tissue. Thus, Smac agonists are promising candidates for cancer therapy by potentiating cytotoxic therapies.

PMID: 12118245 [PubMed - indexed for MEDLINE]

1: Cancer Res 2001 Dec 1;61(23):8513-9

Vaccination of pediatric solid tumor patients with tumor lysate-pulsed dendritic cells can expand specific T cells and mediate tumor regression.

Geiger JD, Hutchinson RJ, Hohenkirk LF, McKenna EA, Yanik GA, Levine JE, Chang AE, Braun TM, Mule JJ.

Department of Surgery, Section of Pediatric Surgery, Section of General Surgery, the Tumor Immunology and Immunotherapy Program, Ann Arbor, Michigan 48109-0245, USA. jgeiger@umich.edu

Dendritic cells (DCs) have been shown to be a promising adjuvant for inducing immunity to cancer. We evaluated tumor lysate-pulsed DC in a Phase I trial of pediatric patients with solid tumors. Children with relapsed solid malignancies who had failed standard therapies were eligible. The vaccine used immature DC (CD14-, CD80+, CD86+, CD83-, and HLA-DR+) generated from peripheral blood monocytes in the presence of granulocyte/monocyte colony-stimulating factor and interleukin-4. These DC were then pulsed separately with tumor cell lysates and the immunogenic protein keyhole limpet hemocyanin (KLH) for 24 h and then combined. A total of 1 x 10(6) to 1 x 10(7) DC are administered intradermally every 2 weeks for a total of three vaccinations. Fifteen patients (ages 3-17 years) were enrolled with 10 patients completing all vaccinations. Leukapheresis yields averaged 2.8 x 10(8) peripheral blood mononuclear cells (PBMC)/kg, and DC yields averaged 10.9% of starting PBMC. Patients with neuroblastoma, sarcoma, and renal malignancies were treated without obvious toxicity. Delayed-type hypersensitivity (DTH) response was detected in 7 of 10 patients for KLH and 3 of 6 patients for tumor lysates. Priming of T cells to KLH was seen in 6 of 10 patients and to tumor in 3 of 7 patients as demonstrated by specific IFN-gamma-secreting T cells in unstimulated PBMCs. Significant regression of multiple metastatic sites was seen in 1 patient. Five patients showed stable disease, including 3 who had minimal disease at time of vaccine therapy and remain free of tumor with 16-30 months follow-up. Our results demonstrate that it is feasible to generate large numbers of functional DC from pediatric patients even in those highly pretreated and with a large tumor burden. The DC can be administered in an outpatient setting without any observable toxicity. Most importantly, we have demonstrated the ability of the tumor lysate/KLH-pulsed DC to generate specific T-cell responses and to elicit regression of metastatic disease.

Publication Types:
- Clinical Trial
- Clinical Trial, Phase I

PMID: 11731436 [PubMed - indexed for MEDLINE]

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1: Clin Cancer Res 2002 Apr;8(4):1021-32

A phase I trial of tumor lysate-pulsed dendritic cells in the treatment of advanced cancer.

Chang AE, Redman BG, Whitfield JR, Nickoloff BJ, Braun TM, Lee PP, Geiger JD, Mule JJ.

Department of Surgery, University of Michigan, Ann Arbor, Michigan 48109-0932, USA. aechang@umich.edu

PURPOSE: The objectives of this study were to assess the toxicity and immunological response induced by the intradermal (i.d) administration of tumor lysate-pulsed dendritic cells (DCs). EXPERIMENTAL DESIGN: Patients with stage IV solid malignancies were treated in cohorts that received 10(6), 10(7), and 10(8) DCs i.d. every 2 weeks for three vaccines. Each vaccine was composed of a mixture of half DCs pulsed with autologous tumor lysate and the other half with keyhole limpet hemocyanin (KLH). Peripheral blood mononuclear cells (PBMCs) harvested 1 month after the last immunization was compared with pretreatment PBMCs for immunological response. Delayed-type hypersensitivity reactivity to tumor antigen and KLH was also assessed. RESULTS: Fourteen patients received all three vaccines and were evaluable for toxicity and/or immunological monitoring. There were no grade 3 or 4 toxicities associated with the vaccines or major evidence of autoimmunity. Local accumulation of CD4(+) and CD8(+) T cells were found at the vaccination sites. There was a significant proliferative response of PBMCs to KLH induced by the vaccine. In 5 of 6 patients, the vaccine resulted in increased IFN-gamma production by PBMCs to KLH in an ELISPOT assay. Using the same assay, 3 of 7 patients' PBMCs displayed increased IFN-gamma production in response to autologous tumor lysate. One patient with melanoma also was observed to have an increased frequency of MART-1- and gp100-reactive CD8(+) T cells after vaccination. By delayed-type hypersensitivity testing, 8 of 9 and 4 of 10 patients demonstrated reactivity to KLH and autologous tumor, respectively. Two patients with melanoma experienced a partial and a minor response, respectively. CONCLUSION: The administration of tumor lysate-pulsed DCs is nontoxic and capable of inducing immunological response to tumor antigen. Additional studies are necessary to improve tumor rejection responses.

Publication Types:
- Clinical Trial

- Clinical Trial, Phase I

PMID: 11948109 [PubMed - indexed for MEDLINE]

1: Int J Urol 2002 Jun;9(6):340-6 Related Articles, Links

online

Dendritic cell immunotherapy for patients with metastatic renal cell carcinoma: University of Tokyo experience.

Azuma T, Horie S, Tomita K, Takahashi T, Tanaka Y, Kashiwase K, Nieda M, Takeuchi T, Ohta N, Shibata Y, Hirai H, Kitamura T.

Departments of Urology, Cell Therapy and Transplantation and Transfusion Medicine, University of Tokyo, Tokyo, Japan.

BACKGROUND: : Dendritic cells (DC) are the most potent antigen-presenting cells and induce host antitumor immunity through the T-cell response. A clinical study of immunotherapy using cultured DC loaded with tumor antigen, for patients with metastatic renal cell carcinoma (RCC) was performed. METHODS: : Dendritic cells were generated by culturing monocytes from peripheral blood for 7 days in the presence of granulocyte-macrophage colony-stimulating factor and interleukin-4. On day 6 the DC were pulsed with lysate from autologous tumor as the antigen and with keyhole limpet hemocyanin (KLH) as immunomodulator. The patients were given four doses of lysate-pulsed DC by intradermal injection with a 2-week interval between doses. Clinical effect and immune response were, respectively, evaluated by radiological examination and delayed-type hypersensitivity (DTH) test. RESULTS: : Three patients were enrolled and the immunotherapy was well tolerated without significant toxicity. The vaccination induced a positive DTH reaction to tumor lysate in two patients and to KLH in all patients. Clinical responses consisted of one case of no change and two cases of progression of disease. However, we did not see a significant reduction of tumor volume in any case. CONCLUSION: : Dendritic cell vaccination can safely induce an immunological response against RCC. Further trials are needed to fully evaluate its efficacy.

PMID: 12110099 [PubMed - in process]

1: Curr Opin Mol Ther 1999 Feb;1(1):72-81

The use of dendritic cells for cancer vaccination.

Esche C, Shurin MR, Lotze MT.

University of Pittsburgh Cancer Institute, Division of Surgical Oncology, 300 Kaufmann Building, 3471 Fifth Avenue, Pittsburgh, PA 15213, USA. esche@altavista.net

Dendritic cells (DC) are the most potent antigen presenting cells (APC) and the only ones capable of presenting novel antigens to naive T-cells. Large numbers of DC can be generated in vitro in the presence of appropriate cytokine cocktails using either adherent peripheral blood mononuclear cells (PBMC) or CD34+ precursors. More than 20 preclinical studies have demonstrated the effectiveness of antigen-loaded DC to mediate antitumor immune responses. Three clinical trials have been reported to date that show DC as a promising tool for the immunotherapy of cancer. However, completion and analysis of randomized trials to establish the appropriate antigen(s), adjuvant(s), dose, route and schedule will be crucial. Future DC-based therapies will include genetic modification of DC, the use of CD34+ precursors, direct delivery of DC to tumors, and application of tumor lysates or apoptotic cells as sources of additional, as yet undefined, antigens.

Publication Types:
- Review
- Review, Academic

PMID: 11249687 [PubMed - indexed for MEDLINE]

☐ 1: Curr Pain Headache Rep 2001 Jun;5(3):250-6 Related Articles, Links

CURRENT reports

Modern management of the cancer anorexia-cachexia syndrome.

Nelson KA.

The Harry R. Horvitz Center for Palliative Medicine (A World Health Organization Demonstration Project), The Taussig Cancer Center of The Cleveland Clinic Foundation, M76, 9500 Euclid Avenue, Cleveland, OH 44195, USA. nelsonk1@ccf.org

The cancer anorexia-cachexia syndrome is common, occurring in 80% of patients with advanced-stage cancer, and it is one of the most frequent causes of death in patients with cancer. It is a complex problem involving abnormalities in protein, carbohydrate, and fat metabolism. Tumors have both direct and indirect effects that result in anorexia and weight loss. The disease burden does not necessarily correlate with the degree of cachexia. In addition to the physical manifestations, the resulting abnormalities have a significant psychologic effect on patients and their families. Although there is no treatment to reverse the process, pharmacologic and nonpharmacologic measures can enhance food intake and improve quality of life.

Publication Types:
- Review
- Review, Tutorial

PMID: 11309213 [PubMed - indexed for MEDLINE]

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☐ 1: Br J Cancer 1997;76(5):606-13 Related Articles, Links

Comment in:
- Br J Cancer. 1999 Mar;79(9-10):1620-1.

Induction of cachexia in mice by a product isolated from the urine of cachectic cancer patients.

Cariuk P, Lorite MJ, Todorov PT, Field WN, Wigmore SJ, Tisdale MJ.

Pharmaceutical Sciences Institute, Aston University, Birmingham, UK.

Urine from cancer patients with weight loss showed the presence of an antigen of M(r) 24,000 detected with a monoclonal antibody formed by fusion of splenocytes from mice with cancer cachexia. The antigen was not present in the urine of normal subjects, patients with weight loss from conditions other than cancer or from cancer patients who were weight stable or with low weight loss (1 kg month(-1)). The antigen was present in the urine from subjects with carcinomas of the pancreas, breast, lung and ovary. The antigen was purified from urine using a combination of affinity chromatography with the mouse monoclonal antibody and reversed-phase high-performance liquid chromotography (HPLC). This procedure gave a 200,000-fold purification of the protein over that in the original urine extract and the material isolated was homogeneous, as determined by silver staining of gels. The N-terminal amino acid sequence showed no homology with any of the recognized cytokines. Administration of this material to mice caused a significant ($P<0.005$) reduction in body weight when compared with a control group receiving material purified in the same way from the urine of a normal subject. Weight loss occurred without a reduction in food and water intake and was prevented by prior administration of the mouse monoclonal antibody. Body composition analysis showed a decrease in both fat and non-fat carcass mass without a change in water content. The effects on body composition were reversed in mice treated with the monoclonal antibody. There was a decrease in protein synthesis and an increase in degradation in skeletal muscle. Protein degradation was associated with an increased prostaglandin E2 (PGE2) release. Both protein degradation and PGE2 release were significantly reduced in mice pretreated with the monoclonal antibody. These results show that the material of M(r) 24,000 present in the urine of cachectic cancer patients is capable of producing a syndrome of cachexia in mice.

☐ 1: J Immunother 2000 Jan;23(1):83-93 Related Articles, Links

Immunomodulatory dendritic cells generated from nonfractionated bulk peripheral blood mononuclear cell cultures induce growth of cytotoxic T cells against renal cell carcinoma.

Hinkel A, Tso CL, Gitlitz BJ, Neagos N, Schmid I, Paik SH, deKernion J, Figlin R, Belldegrun A.

Department of Urology, University of California, Los Angeles, USA.

Dendritic cells (DCs) loaded with tumor antigens have the potential to become a powerful tool for clinical cancer treatment. Recently, the authors showed that a tumor-specific immune response can be elicited in culture via stimulation with autologous renal tumor lysate (Tuly)-loaded DCs that were generated from cytokine-cultured adherent peripheral blood mononuclear cells (PBMCs). Here, the authors show that immunomodulatory DCs can be generated directly from nonfractionated bulk PBMC cultures. Kinetic studies of DC differentiation and maturation in PBMC cultures were performed by monitoring the acquisition of DC-associated molecules using fluorescence-activated cell sorting analysis to determine the percentage of positive immunostained cells and the mean relative linear fluorescence intensity (MRLFI). Compared with conventional adherent CD14+ cultures, which have mostly natural killer, T, and B cells removed before cytokine culture, bulk PBMC cultures exhibited an early loss of CD14+ cells (day 0 = 78.8%, day 2 = 29.6% versus day 0 = 74%, day 2 = 75%) with an increase in yield of mature DCs (DC19- CD83+) (day 5 = 17%, day 6 = 21%, day 7 = 22% versus day 5 = 11%, day 6 = 15%, day 7 = 23%). Although a comparable percentage of DCs expressing CD86+ (B7-2), CD40+, and HLA-DR+ were detected in both cultures, higher expression levels were detected in DCs derived from bulk culture (CD86 = MRLFI 3665.1 versus 2662.1 on day 6; CD40 = MRLFI 1786 versus 681.2 on day 6; HLA-DR = MRLFI 6018.2 versus 3444.9 on day 2). Cytokines involved in DC maturation were determined by polymerase chain reaction demonstrating interleukin-6 (IL-6), IL-12, interferon-gamma, granulocyte-macrophage colony-stimulating factor, and tumor necrosis factor-alpha mRNA expression by bulk culture cells during the entire 9-day culture period. This same cytokine mRNA profile was not found in the conventional adherent

DC culture. Autologous renal Tuly (30 micrograms protein/10(7) PBMCs) enhanced human leukocyte antigen expression by DCs (class I = 7367.6 versus 4085.4 MRFLI; class II = 8277.2 versus 6175.7 MRFLI) and upregulated cytokine mRNAs levels. Concurrently, CD3+ CD56-, CD3+ CD25+, and CD3+ TCR+ cell populations increased and cytotoxicity against autologous renal cell carcinoma tumor target was induced. Specific cytotoxicity was augmented when cultures were boosted continuously with IL-2 (20 U/mL biological response modifier program) plus Tuly stimulation. These results suggest that nonadherent PBMCs may participate in enhancing DC maturation. Besides the simplicity of this culture technique, bulk DC cultures potentially may be used with the same efficiency as conventional purified DCs. Furthermore, bulk culture-derived DCs may be used directly in vivo as a tumor vaccine, or for further ex vivo expansion of co-cultured cytotoxic T cells to be used for adoptive immunotherapy.

PMID: 10687141 [PubMed - indexed for MEDLINE]
